# I. THE CONVERSION OF ARYL ACETYLENES INTO HINDERED ARYL ACRYLIC ACIDS
# II. SOME SYNTHETIC HOMOLOGS OF TETRAHYDROCANNABINOL

BY

CLEMENT WALTER THEOBALD

B.A., University of Nebraska, 1939
M.A., University of Nebraska, 1940

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
CHEMISTRY IN THE GRADUATE SCHOOL OF
THE UNIVERSITY OF ILLINOIS, 1943

URBANA, ILLINOIS

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# PART I

# THE CONVERSION OF ARYL ACETYLENES INTO HINDERED ARYL ACRYLIC ACIDS

## Introduction

A number of aryl olefins of the β-aryl-β-chloroacrylic acid type have been prepared and resolved by virtue of restricted rotation between an aromatic-aliphatic single bond. The effect of variation of the *ortho* substituents in the aryl nucleus on racemization rate has been studied for the compounds in which the aryl group was the bromomesityl,[1,2] bromotriethylphenyl,[2] 2-methoxy-4,6-dimethyl-5-chlorophenyl,[3] and α-(β-methylnaphthyl)[4] radical. The β-chloro-β-aryl-α-methylacrylic acids corresponding to these acids have been resolved and found to be more stable than their lower homologs. The synthetic procedure by which these acrylic acid derivatives were synthesized does not allow a wide variation of the β-substituent, and indeed only one compound has been resolved which contained a β-subsituent other than the chlorine atom.[5] It was the purpose of this investigation to develop a synthetic procedure by which the β-substituent could be varied widely, and to study the effects of such variations on the restriction of rotation, as evidenced by the effect on the half-life period of racemization. The procedure developed involved the synthesis of an arylpropiolic acid, to which a variety of reagents could be added to give β-substituted acrylic acids. It was hoped also that the *cis-trans* isomer of some of the compounds, whose resolution had already been effected, might be prepared by this new procedure. However, this objective was not realized.

## Experimental and Discussion

Mesitylacetylene was synthesized from acetomesitylene through the intermediate $\alpha$-chlorovinylmesitylene.[6] Mesitylpropiolic acid was prepared from this acetylene by treatment with ethylmagnesium bromide and carbon dioxide. Hydrogen bromide and hydrogen chloride were added across the triple bond, but the compounds so obtained were not suitable for resolution.

By an analogous procedure bromomesitylpropiolic acid was prepared from acetobromomesitylene. Addition of hydrogen chloride to bromomesitylpropiolic acid gave a compound identical with the acid prepared by Miller[2] which had previously been resolved. Hydrogen bromide likewise was added, giving $\beta$-chloro-$\beta$-(3-bromo-2,4,6-trimethylphenyl)-acrylic acid. Only one of the two possible *cis-trans* isomers was obtained. Resolution of this acrylic acid was effected through its quinine salt, and the *d*- and *l*- acids were obtained with a specific rotation of $+33.5°$ and $-37.2°$. The *l*-acid racemized in boiling *n*-butanol with a half-life of sixty-four hours, as compared to three and one-third hours for the $\beta$-chloro analog.[2]

Methyl $\beta$-methoxy-$\beta$-(3-bromo-2,4,6-trimethylphenyl)-acrylate was prepared from methyl bromomesitylpropiolate by the addition of sodium methylate in methyl alcohol, and by the action of diazomethane on bromomesitoylacetic acid. The two esters were identical. Resolution of the acid obtained by saponification was attempted by means of quinine and brucine, but in both cases only one well-defined crystalline salt was obtained; decomposition of these salts gave an optically inactive acid.

Isodurylpropiolic acid was synthesized from the acetylene obtained from acetoisodurene by the above procedure. Addition of hydrogen chloride to the propiolic acid gave $\beta$-chloro-$\beta$-(2,3,4,6-tetramethylphenyl)-acrylic acid, which was identical with this acid prepared from isoduroylacetic acid. The optical antipodes were separated by means of their quinine salts. The *d*- and *l*-acids had specific rotations of $+35.2°$ and $-36.6°$ re-

spectively. The *l*-acid was racemized in boiling *n*-butanol with a half-life of 174 minutes. The analogous bromomesityl compound had a half-life of 200 minutes.[2]

Hydrogen iodide was added to isodurylpropiolic acid in aqueous solution at room temperature, but the resolution of this compound was not investigated. Iodine would also add to the triple bond of isodurylpropiolic acid, but the diiodo acid produced was quite unstable and could not be purified successfully. It was concluded from the ease with which the addition of these reagents occurred that the reactions of di-*ortho*-substituted arylpropiolic acids could be expected to parallel the reactions of phenylpropiolic acid, and hence lead to a large variety of $\beta$-substituted-$\beta$-arylacrylic acids suitable for resolution.

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## PART II

## SOME SYNTHEIC HOMOLOGS OF TETRAHYDROCANNABINOL

### Introduction

The discovery that tetrahydrocannabinol, obtained from the isomerization of cannabidiol and the synthetic isomer with a double bond conjugated with the aromatic nucleus had a typical marihuana activity has led to a study of the variation of structure on the physiological potency. It was the purpose of this investigation to continue this line of study by varying the substituents in aliphatic ring.

## Experimental and Discussion

High-pressure catalytic reduction of *m*-ethyl-3,5-dimethyl-, and 3,4-dimethylphenol gave the corresponding cyclohexanol in nearly quantitative yield. The cyclohexanones were prepared from the alcohols by oxidation with sodium dichromate in sulfuric acid. The ketones reacted with ethyl oxalate in the presence of sodium ethoxide to give glyoxylic esters, which were converted to the carbethoxycyclohexanones by pyrolysis over powdered soft glass and iron filings. Ethyl 5-ethylcyclohexanone-2-carboxylate was condensed with olivetol[1] to give 1-hydroxy-3-*n*-amyl-9-ethyl-7,8,9,10-tetrahydro-6-dibenzopyrone. Methylmagnesium iodide converted this pyrone to 1-hydroxy-3-*n*-amyl-9-ethyl-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran which had a marihuana potency of 0.22 ± 0.02. Ethyl 4,5-dimethylcyclohexanone-2-carboxylate was similarly converted through the intermediate pyrone to 1-hydroxy-3-*n*-amyl-6,6,8,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran having a hashish activity of 0.11 ± 0.03. 1-Hydroxy-3-*n*-amyl-6,6,7,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran was obtained from ethyl 3,5-dimethylcyclohexanone-2-carboxylate in an analogous manner. This last pyran had a potency of 0.75± 0.08, but the typical marihuana activity was accompanied by a convulsant action.

*d*-1-Hydroxy-3-*n*-hexyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone was prepared by the condensation of *d*-ethyl 5-methylcyclohexanone-2-carboxylate with 5-*n*-hexylresorcinol. The *d*-pyran was prepared by the action of methylmagnesium iodide on this pyrone and has been submitted for a physiological study, the results of which have not been completed. *l*-3-Methylcyclohexanone was prepared by resolution of the racemic ketone with the bisulfite addition compound of *l*-$\alpha$-phenylethylamine. Oxalation and pyrolysis gave the *l*-carbethoxy ketone which was condensed with 5-*n*-hexylresorcinol to *l*-1-hydroxy-3-*n*-hexyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.

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## VITA

The author was born March 24, 1918, in Lincoln, Nebraska, where he received his elementary schooling. In 1935 he graduated from Lincoln High School. He attended the University of Nebraska during the academic years 1935-1940, receiving the degrees of Bachelor of Arts with distinction in 1939, and Master of Arts in 1940. During the year 1938-1939 he held the George Borrowman Scholarship, and was graduate teaching assistant. He entered the University of Illinois in 1940 as graduate teaching assistant, received a University of Illinois Fellowship for the year 1941-1942, and the Eastman Kodak Fellowship for 1942-1943.

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